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SHORT COMMUNICATION

Ketoconazole Treatment of Gonadotropin Independent Precocious Puberty in Girls with McCune-Albright Syndrome: A Preliminary Report

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ABSTRACT

McCune-Albright syndrome (MAS) in girls is characterized by gonadotropin independent precocious puberty (GIPP). This form of GIPP is resistant to therapy with GnRH analogues. As an alternative treatment, we successfully used ketoconazole 200 mg t.i.d. orally in two girls with MAS, GIPP and advanced bone age Ketoconazole led to rapid control of GIPP with cessation of menses and regression of pubertal signs in both patients. Ketoconazole was temporarily interrupted in one patient due to pruritis but later restarted without problem. After 1 year of therapy both patients have remained free of menses, progression of puberty and other side effects. Repeat sonography on ketoconazole revealed continued presence of ovarian cysts. Our preliminary experience indicates the safety and effectiveness of ketoconazole as a therapy for GIPP with potential advantages over previously used modes of treatment. Longer use of ketoconazole to suppress GIPP is required to determine whether this therapy can prolong linear growth with enhancement of final height.

INTRODUCTION

McCune-Albright syndrome (MAS) is characterized by the combination of polyostotic fibrous dysplasia, "coast of Maine" skin markings and autonomous endocrine hyperfunction. Precocious puberty is the most common endocrinopathy in this syndrome[1], which in girls is typified by estrogen hypersecretion from ovarian cysts which function independently of normal hypothalamic-pituitary control[2]. Autonomous ovarian estrogen release is caused by a G protein mutation in the gonadotropin receptor with constitutive activation of estrogen secreting cells[3,4]. Circulating gonadotropin levels in MAS are reduced and there is a suppressed response of LH and FSH to GnRH stimulation[5].

Gonadotropin independent precocious puberty (GIPP) in MAS makes therapy with GnRH analogues futile[2,6]. Medroxyprogesterone has been used to stop menses but does not halt bone age advancement and treatment may be accompanied by undesirable side effects[7]. Testolactone has been reported to interrupt estrogen production from ovarian cysts with remission of puberty[8], but this therapy requires large doses four times a day, and therapy is not always effective.

Ketoconazole has been safely and successfully used to treat boys with GIPP by blocking gonadal steroidogenesis[9-11]. Similar to MAS, testotoxicosis is due to an activating mutation in testicular Leydig cells[12]. We applied this therapeutic experience to successfully interrupt precocious puberty in two girls with MAS during a year of therapy.

PATIENT REPORTS AND RESULTS

Patient 1 had white European ancestry. She developed thelarche at age 2, pubic hair and accelerated growth were noted at 5 years. At age 5½ yr an irregularly bordered café-au-lait skin marking 3 cm in diameter was reported on examination. Pelvic ultrasound revealed a 10 mm

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left ovarian cyst, bone scan showed polyostotic fibrous dysplasia. LH and FSH responses to GnRH were blunted; estradiol was <50 pg/ml.

At 6½ years she developed vaginal bleeding every other month accompanied by increased growth velocity, bone age was 11 years, breast stage II, pubic hair III. Repeat GnRH test showed a blunted LH and FSH response; ultrasound revealed bilateral cystic ovaries. She began testolactone which was gradually increased to 300 mg q.i.d., with cessation of vaginal bleeding and regression in breast development to Tanner 1 and pubic hair I. After 11 months of testolactone she again had breast budding, bone age was 12 years. She complained of the difficulty of taking 6 tablets q.i.d. Testolactone was discontinued. She started ketoconazole 200 mg p.o. t.i.d. with complete resolution of signs of puberty. After 1 year of ketoconazole therapy she has had no signs of puberty, growth velocity slowed to 3.5 cm/yr (height 90%), bone age was 12 years at chronologic age 8½ years. Repeat liver enzymes were normal, 17OH-progesterone was 198 ng/dl (normal <90), "sensitive" estradiol level was 7 pg/ml. Ultrasonography revealed a cyst in the right ovary and a juvenile configuration of the uterus.

Patient 2 was African-American. She was noted to have extensive "coast of Maine" café-au-lait skin markings at birth. She began to have vaginal bleeding for 1½ days at 8 months of age and another episode at 19 months. At 21 months, she fractured her hip and X-ray studies revealed polyostotic fibrous dysplasia.

At age 3-$^{11}/_{12}$ years, she began to have vaginal bleeding every other month with breast enlargement, bone age was 4-$^{2}/_{12}$ yr. She was given Depo provera 0.5 ml i.m. every 3-4 months as needed, which stopped the vaginal bleeding. GnRH stimulation at age 4-$^{7}/_{12}$ years showed a prepubertal response of LH and FSH. She was then observed without further therapy until age 5-$^{9}/_{12}$ years when she again had periodic episodes of vaginal bleeding with advancement to Tanner 3 breast and Tanner 2 pubic hair. BA was 7-$^{10}/_{12}$ years. Pelvic ultrasound showed left ovarian enlargement with a prominent follicle. Estradiol level was elevated at 39.3 pg/ml; a GnRH test showed a blunted response of LH and FSH. Testolactone was started at age 6-$^{2}/_{12}$ yr and increased to 300 mg p.o. q.i.d. over a 4 week period. Episodes of vaginal bleeding stopped and breast stage regressed to Tanner 2. After week 6 of therapy, testolactone was stopped due to the development of nasal bleeding, recurrent vomiting and extreme behavior changes with possible hallucinations. These symptoms abated with discontinuation of testolactone.

At age 7-$^{11}/_{12}$, she resumed intermittent episodes of vaginal bleeding, and breast stage progressed to Tanner 4, bone age was 10 years. A GnRH test revealed a blunted LH/FSH response; estradiol level was 228.8 pg/ml. Pelvic ultrasound showed multiple cysts in the right ovary. She started ketoconazole at 200 mg p.o. t.i.d. with no further vaginal bleeding and breast regressed to Tanner stage 3. Ketoconazole therapy was interrupted after the development of a pruritic rash. Off ketoconazole she again had vaginal bleeding. She resumed ketoconazole at a dose of 200 mg p.o. t.i.d with cessation of menses. An estradiol level measured by sensitive assay during ketoconazole therapy was 6 pg/ml.

At age 8-$^{5}/_{12}$ years a bone fracture necessitated in-patient surgical treatment at another hospital, and compliance with ketoconazole was erratic; after 2 months she again had vaginal bleeding. Bone age was 11 years at a chronologic age of 8-$^{8}/_{12}$ years.

DISCUSSION

The short term goals of therapy for GIPP in girls with MAS are cessation of menses and precocious pubertal development. The long term objective of therapy is to restrain bone age advancement in order to permit more time for linear growth and enhance final attained height. The therapeutic agent should be safe and convenient to administer.

Our preliminary experience in two patients with MAS suggests that ketoconazole can be safely and successfully applied to treat GIPP due to functional ovarian cysts. Ketoconazole treatment led to rapid cessation of menstrual bleeding, regression of secondary sexual characteristics, reduction of estradiol levels and decrease of bone age advancement. However, ketoconazole did not appear to halt the occurrence of ovarian cysts. Patients found t.i.d. dosing of a single pill (200 mg) of ketoconazole to be much more convenient and easier to comply with than the large doses and q.i.d. dosing of testolact-

one. Furthermore ketoconazole could be used in situations in which adverse effects prohibited continued use of testolactone (patient 2).

Ketoconazole inhibits steroid biosynthesis by blocking gonadal mitochondrial cytochrome P-450 enzymes, including 17,20-desmolase as well as 11, 17 and 18 hydroxylation steps[13]. Clinically this inhibition can be followed by observing an increase in 17OH-progesterone. Experience has indicated that clinically relevant adrenal insufficiency does not occur[11], probably due to compensatory increases in ACTH and renin secretion. However, it is prudent to monitor adrenal function periodically during ketoconazole therapy.

Ketoconazole has been associated with reversible liver toxicity in 1/100,000 cases and this side effect can be monitored by measurement of liver enzymes[11]. Pruritus is also associated with ketoconazole but appears to be transient and responds to interruption of therapy. Pruritis may not recur with retreatment, as we observed in Patient 2.

Whether ketoconazole will be a safe and effective chronic therapy for GIPP in MAS and whether it can achieve the long-term goals of prolonged linear growth with enhancement of adult height will require further observation and a larger number of patients. Our preliminary experience is encouraging and indicates the safe short term effectiveness of ketoconazole as an alternative therapy for GIPP in MAS with advantages over previously used modes of treatment.

REFERENCES

1. Mauras N, Blizzard RM. The McCune Albright syndrome. Acta Endocrinol 1986; 279 (Suppl): 207-217.
2. Wheeler MD, Styne DM. Diagnosis and management of precocious puberty. Pediatr Clin N Am 1990; 37: 1255-1271.
3. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegal AM. Activating mutations of the stimulatory G protein in the McCune Albright syndrome. N Engl J Med 1991; 325: 1688-1695.
4. Ringel MD, Schwindinger WF, Levine MA. Clinical implications of genetic defects in G proteins. The molecular basis of McCune Albright and Albright hereditary osteodystrophy. Medicine 1996; 75: 171-184.
5. Foster CM, Ross JL, Shawker T, Pescovitz OH, Loriaux DL, Cutler GB Jr, Comite F. Absence of pubertal gonadotropin secretion in girls with McCune-Albright syndrome. J Clin Endocrinol Metab 1984; 58: 1161-1165.
6. Foster CM, Comite F, Pescovitz OH, Ross JL, Loriaux DL, Cutler GB Jr. Variable response to a long-acting agonist of lutenizing hormone releasing hormone in girls with McCune-Albright syndrome. J Clin Endocrinol Metab 1984; 59: 801-805.
7. Wheeler MD. Update on therapy for precocious puberty. Compr Ther 1994; 20: 351-355.
8. Feuillan PP, Jones J, Cutler GB Jr. Long term Testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. J Clin Endocrinol Metab 1993; 74: 647-651.
9. Holland FJ, Fishman L, Bailey JD, Fazekas AT. Ketoconazole in the management of precocious puberty not responsive to LHRH-analogue therapy. N Engl J Med 1985; 312: 1023-1028.
10. Holland FJ, Kirsch SE, Selby R. Gonadotropin-independent precocious puberty ("testotoxicosis"): influence of maturational status on response to ketoconazole. J Clin Endocrinol Metab 1987; 64: 328-333.
11. Holland FJ. Gonadotropin-independent precocious puberty. Endocrinol Metab Clin N Am 1991; 20: 191-210.
12. Yano K, Hidaka A, Saji M, Polymeropoulos MH, Okuno A, Kohn LD, Cutler GB Jr. A sporadic case of male-limited precocious puberty has the same constitutively activating point mutation in lutieinizing hormone/choriogonadotropin receptor gene as familial cases. J Clin Endocrinol Metab 1994; 79: 1818-1823.
13. DiMattina M, Maronian N, Ashby H, Loriaux DL, Albertson BD. Ketoconazole inhibits multiple steroidogenic enzymes involved in androgen biosynthesis in the human ovary. Fertil Steril 1988; 49: 62-65.